



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2016

Allergies then and now

Favrot, Claude

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-126579>

Conference or Workshop Item

Originally published at:

Favrot, Claude (2016). Allergies then and now. In: British Veterinary Dermatology Study Group, London, Great Britain, 24 October 2016 - 25 October 2016, s.n..

ALLERGIES THEN AND NOW

Prof Dr Claude Favrot

A quick glance at the past....

Atopy was first described 1923 by Coca and Cooke and was defined as a familial type of allergy associated with an immediate type of hypersensitivity [1]. The first description of atopy in dogs was made in 1939 while the first description of flea allergy dates from 1938 and the first review article on allergies in animals from 1941 [2, 3]. Human reaginic IgE antibodies were described simultaneously in 1967 by Johansson and Ishizaka [4]. The canine counterpart was described in 1971 by Schwartzmann and Halliwell [5]. At that time, the pathogenesis of atopic dermatitis was described as a pure IgE reaction: "The clinical signs are due to the formation of reaginic sensitizing IgE antibodies.....that fixes to circulating basophils or tissue mast cells. When the cell bound antibody comes in contact with the antigen, it causes degranulation of the cell [6] causing the liberation of vasoactive amines such as histamine, serotonin and kinins" [6]. The same author estimated the incidence of this condition to 15%, which was higher than the incidence in human beings at the same period [6]. The clinical signs were directly caused by the effects of the vasoactive amines and were described as edema, erythema and pruritus [6]. Chamberlain mentioned that the feet, the toes, the eyelids, ear pinnae and canals, groin and perineal area were mainly affected and that the course of the disease might be chronic, periodic, persistent or sporadic. He also described the possible lichenification of the skin in chronic patients. As well, he noticed that the clinical signs were reversible when glucocorticoids were applied but that the signs relapsed when treatment is discontinued [6]. Atopic dermatitis was caused by intrinsic (heredity, emotional and psychogenic factors, hormonal aberrations and autoimmunity) and extrinsic (seasonal and non-seasonal inhalants, ingestants, endoparasites and microbes) factors. As far as the environmental allergens were concerned, pollens, house dust, fleas and foods were considered to be the most relevant for canine atopic dermatitis [7]. The diagnosis of the condition was mainly based on the history of the patients, the clinical examination and laboratory tests. Chamberlain considered that the main features were family history, eosinophilia, pruritus, the relapsing course of the disease and the improvement with gluco-corticoids drugs [6]. As far as laboratory tests were concerned, he recommended skin scrapings, bacterial and fungal cultures, blood and urinalyses and skin biopsies. Once the allergy was confirmed and/or resembling diseases, especially ectoparasites, ruled out, it was recommended to evaluate the role of the food and to perform skin testing. Skin testings were strongly recommended and were mainly carried out with mixes (Grasses, trees, weeds, molds, epidermals, feathers, insects and bacteria) while only ragweed, flea, cotton, kapok and house dust were tested separately [8]. It is worth mentioning, that, in the same article, the authors discussed the drawbacks and advantages of prick test, patch test and provocation exposure, the latter, especially for foods. In 1974, the recommended treatment of canine atopic dermatitis were glucocorticoids, antihistamines (even

though efficiency was considered matter of debate) an allergen-specific immunotherapy [9, 10]. Some other somewhat more surprising recommended drugs were also mentioned such as periactin and cromoglycate [10]. It is also worth mentioning that, in 1974, the relation between food allergy and atopic dermatitis as well as the role of staphylococcal infections, fungal and bacterial hypersensitivities were also discussed [11-14].

2016: are we yet so far away?

Since 1974, about 750 PubMed-indexed articles on canine atopic dermatitis have been published. We may consequently have the impression that we have accomplished major progresses. But is it that true?

Atopic dermatitis prevalence:

More than 40 years after the article by Chamberlain mentioned above, we still do not have a reliable study on the prevalence of this disease [15]! Many authors still regard an AD prevalence of 15% (estimation by Chamberlain) as plausible but nobody was able to prove it yet!

Environmental factors and AD

As described above, early articles focused mainly on the role of environmental allergens. As well, food and microbes were mainly regarded as sources of allergens.

One should remember that the so-called “hygiene hypothesis” was first described in 1989 [16]. Numerous studies carried out in humans have suggested that other environmental factors such as microbes, parasites, endotoxins may play a driving role in the development of human AD. Some studies have also been carried out in dogs and shed a new light on this aspect of the AD pathogenesis. In particular, some studies support, although weakly, the protective role toward the development of canine AD, of the contact with microbes [17-20].

Genetics

We noticed already that familial predisposition was recognized very early in human and dogs with AD. A link between heredity and the development of the disease was clearly mentioned by Chamberlain in 1974. Numerous studies have now been published and proved the association of human atopic dermatitis and some genetic mutations, especially filaggrin [21]. In dogs, breed predisposition were clearly established [17]. Several genome-wide linkage and association studies have been published but only one gene, Plakophilin 2, was clearly associated with AD in German shepherd dogs [22]. It is very likely that the great diversity of canine breeds complicated these studies.

Allergens

The role of environmental, microbial and food allergens was always suspected. However tests were mainly carried out with mixes. More importantly, in 1974, most tests for indoor allergens

were made on dust extracts and not on mites. It is now clear that the most important allergens in house dust are mites, especially *Dermatophagoides farinae* (DF). Since 2000, DF canine major and minor allergens have been described. In human, testing are now often carried out on allergens and not anymore on whole extracts of mites. This hurdle is still not cleared in veterinary allergology.

As well, in human allergology, the so-called “component- resolved diagnosis” allows the allergist not only to identify the main allergens of each patient but also, in some cases, to recognize the primary sensitizer [23, 24]. Veterinary allergists are still far away from this approach.

Pathogenesis

Our view of the pathogenesis of AD is increasingly complex. We do not regard anymore AD as a pure IgE reaction. First, a lot of attention has been paid to the role of epidermal barrier [25]. The identification of the filaggrin gene mutation as one of the most important genetic factor associated with AD in humans has shed some light on a previously ignored important aspect of the disease. In fact, numerous children with AD have a primary defective stratum corneum. This impaired barrier is known to facilitate the penetration of allergens but also the penetration of microbes. In dogs, despite the discovery of plakophilin mutation in atopic German shepherd and some studies showing a lack of expression of stratum corneum proteins in allergic individuals, it is still unclear whether epidermal barrier dysfunction is a primary or secondary change. Pruritus is one of the most constant and earlier signs of AD. Pruritus leads naturally to secondary impairment of the epidermal barrier. As well, some of the major DF allergens are enzymes that may also destroy the upper layer of the skin epithelium. Last but not least secondary bacterial and yeast infections may also contribute to a defective protection of the living epidermis. Some additional studies are clearly mandatory to determine if the defective barrier is primary or secondary in dogs. It should be kept in mind that both scenarios may coexist in some patients while one or the other may be more important in other patients.

The old view of AD favoured a Th2 type pathogenesis of AD. The Th2 phenotype promote the production of allergen-specific IgE, the recruitment of inflammatory cells such as eosinophils and the activation of hypersensitivity- associated cells such as mast cells. Nowadays it appears however obvious that other phenotypes and cell types also play a major role in the development of the disease. The Th1 phenotype, in example, is clearly involved in the more chronic stages of AD. As well, some studies have shown that T regulatory cells are also important[26]. Some other T cells subclasses such Th22 and Th17 are also involved in human AD even though their role in canine AD is less studied.

In addition, the use of microarray gene expression has enabled the identification of previously ignored cytokine and inflammatory factors that are likely to be involved. For example, it has been recently shown that one of the earlier activated gene in sensitized dogs is IL31, which is

known to code for highly pruritogenic cytokine. This shows that pruritus is not only a consequent of the atopic disease but also of the triggering factor of a very complex cascade.

The role of IgE itself is questioned [27]. First, the above mentioned studies suggested that allergen-specific IgE may be a consequence of the atopic disease and not the primary cause. In this regard, the identification, first in humans than in dogs, of patients with an atopic phenotype but no demonstrable allergen-specific IgE, the so-called intrinsic or atopic like disease, may be regarded as supportive. One more time, it should be kept in mind that AD is a protean and complex disease and that not all AD patients have the same disease course and causes.

All in all, we are still, especially in veterinary allergy, from a global understanding of this condition. We have made some progress but, unfortunately, these progresses did not make the picture clearer.

The role of microbial factors.

As mentioned earlier, the role of microbes, especially bacteria, in AD was very early recognized. The role of malassezia was identified later [28]. Microbes are now considered to play a very complex role in the development of the disease. First, they could be protective in some circumstances. But when the disease develops they contribute to the worsening of the pruritus and the impairment of the epidermal barrier. Last but not least, they are also regarded as potential allergens in some patients. It is also important to mention that a lot of attention is now paid to the microbiome. New amplification and sequencing techniques allowed to uncover the incredible complexity and richness of the skin flora. It has been shown that the microbiome of atopic dogs is far less complex than the counterpart in healthy individuals [29]. Further studies are however needed to draw conclusions of these findings.

Clinical signs and diagnosis

As written above, canine AD was first diagnosed in 1939 and the clinical signs of the condition were already very well described in the early fifties. The only important change in the description of the condition is the rarer association with signs of hay fever. We now know that numerous AD dogs only present with skin changes.

We have shown above that the diagnosis of AS was based on the exclusion of resembling diseases such as ectoparasites and on the presence of specific features such as relapsing course, pruritus or response to glucocorticoids. In this regard, the only major changes was the introduction, first in humans, then in animals of diagnostic criteria. It should however be kept in mind that the best validated sets are associated with sensitivity and specificity around 80% and that these criteria cannot be regarded as very accurate [30]. In fact, they are mainly used in the context of clinical studies to ensure recruitment homogeneity. These sets of criteria have also been developed in specialized practices and have not been validated for the use in general practices [31].

Treatment and management

Glucocorticoids, antihistamines and allergen-specific immunotherapy were the recommended tools in 1974. During these four decades numerous drugs were tested, advocated, promoted but glucocorticoids and ASIT are still widely used. ASIT is still considered as the sole etiologic treatment of AD. Recently some new routes for ASIT such as ILIT and SLIT (intralymphatic and sub-lingual, respectively) have been described and seem promising. As well some protocol for rush immunotherapy have been described. But as mentioned above, the next step, in veterinary allergology, should be the use of allergen-based-ASIT.

Only two drugs have really changed the management of canine AD in the last forty years: Cyclosporine A and Oclacitinib [32-34]. The former has the big advantage to be used on the long-term with limited side-effects and to be tapered relatively quickly. The latter controls pruritus very quickly and does not seem to induce severe side-effects.

It could be anticipated that other drugs will soon be available. This is mainly because atopic diseases in humans (atopic dermatitis but also hay fever, food allergy and asthma) are considered to be one of the most prevalent conditions and that a lot of research on these disease is currently made. As the dog is considered as the best natural model for this human conditions, it will profit from this extensive research.

In this regard, the use of anti-cytokine or anti-immunoglobulins antibodies are extremely promising.

What else?

As mentioned several times before, AD is a protean, multifaceted disease and we have now understood that a more global, and holistic approach of the management is needed. In this regard, the role of food, epidermal barrier treatments, anti-bacterial peptides should be more extensively investigated and will probably be implemented in the near future for a better management of atopic patients.

1. Coca, A.F. and R.A. Cooke, *On the classification of the phenomenon of hypersensitiveness*. Journal of Immunology, 1923.
2. Kissileff, A., *The dog flea as a causative agent in summer eczema*. Journal of American Veterinary Medicine Association, 1938. **9**: p. 21-27.
3. Wittich, F.W., *Spontaneous allergy in the lower animal*. Journal of Allergy, 1941. **62**: p. 236-242.
4. Stannworth, D.R., *The discovery of IgE*. Allergy, 1993. **48**(67-71).
5. Schwartzmann, R.M., J.H. Rockey, and R.E.W. Haliweell, *Canine reaginic antibody characterization of the spontaneous antiragweed and induced antidinitrophenyl reaginic antibodies of the atopic dog*. Clinical and Experimental Immunology, 1971. **9**: p. 549-569.
6. Chamberlain, K.W., *Atopic (allergic) dermatitis*. Veterinary Clinics of North America, 1974. **4**(1): p. 29-39.

7. Lorenz, M.D., *Environmental allergens in small animal hypersensitivity disorders*. Veterinary Clinics of North America, 1974. **4**(1): p. 41-46.
8. Chamberlain, K.W., *Diagnostic methods in allergic disease*. Veterinary Clinics of North America, 1974. **4**(1): p. 47-56.
9. Chamberlain, K.W., *Biological management of the allergic patient*. Vet Clin North Am Small Anim Pract, 1974. **4**(1): p. 65-77.
10. Schwark, W.S., *Pharmacologic management of allergic diseases*. Veterinary Clinics of North America, 1974. **4**(1): p. 57-64.
11. Baker, E., *Food allergy*. Vet Clin North Am Small Anim Pract, 1974. **4**(1): p. 79-89.
12. Baker, E., *Staphylococcal disease*. Vet Clin North Am Small Anim Pract, 1974. **4**(1): p. 107-117.
13. Baker, E., *Fungal allergy*. Vet Clin North Am Small Anim Pract, 1974. **4**(1): p. 119-123.
14. Scherago, M., *Bacterial allergy*. Vet Clin North Am Small Anim Pract, 1974. **4**(1): p. 91-105.
15. Hillier, A. and C.E. Griffin, *The ACVD task force on canine atopic dermatitis (I): incidence and prevalence*. Vet Immunol Immunopathol, 2001. **81**: p. 147-152.
16. Strachan, D.P., *Hay fever, hygiene, and household size*. BMJ, 1989. **299**(6710): p. 1259-60.
17. Bizikova, P., et al., *Review: Role of genetics and the environment in the pathogenesis of canine atopic dermatitis*. Vet Dermatol, 2015. **26**(2): p. 95-e26.
18. LooRINGH van Beeck, F.A., et al., *Inverse association between endotoxin exposure and canine atopic dermatitis*. The Veterinary Journal, 2011. **190**(2): p. 215-219.
19. Meury, S., et al., *Role of the environment in the development of canine atopic dermatitis in Labrador and golden retrievers*. Vet Dermatol, 2011. **22**(4): p. 327-34.
20. Nodtvedt, A., et al., *A case-control study of risk factors for canine atopic dermatitis among boxer, bullterrier and West Highland white terrier dogs in Sweden*. Vet Dermatol, 2007. **18**(5): p. 309-15.
21. Morar, N., et al., *The genetics of atopic dermatitis*. J Allergy Clin Immunol, 2006. **118**(1): p. 24-34; quiz 35-6.
22. Tengvall, K., et al., *Genome-wide analysis in German shepherd dogs reveals association of a locus on CFA 27 with atopic dermatitis*. PLoS Genet, 2013. **9**(5): p. e1003475.
23. Pittner, G., et al., *Component-resolved diagnosis of house-dust mite allergy with purified natural and recombinant mite allergens*. Clin Exp Allergy, 2004. **34**(4): p. 597-603.
24. Valenta, R., T. Twaroch, and I. Swoboda, *Component-resolved diagnosis to optimize allergen-specific immunotherapy in the Mediterranean area*. J Invest Allergol Clin Immunol, 2007. **17 Suppl 1**: p. 36-40.
25. Santoro, D., et al., *Review: Pathogenesis of canine atopic dermatitis: skin barrier and host-micro-organism interaction*. Vet Dermatol, 2015. **26**(2): p. 84-e25.
26. Pucheu-Haston, C.M., et al., *Review: Lymphocytes, cytokines, chemokines and the T-helper 1-T-helper 2 balance in canine atopic dermatitis*. Vet Dermatol, 2015. **26**(2): p. 124-e32.
27. Pucheu-Haston, C.M., et al., *Review: The role of antibodies, autoantigens and food allergens in canine atopic dermatitis*. Vet Dermatol, 2015. **26**(2): p. 115-e30.
28. Mason, K.V. and A.G. Evans, *Dermatitis associated with Malassezia Pachydermatis in 11 dogs*. Journal of American Animal Hospital association, 1991. **27**(13-18).
29. Bradley, C.W., et al., *Longitudinal Evaluation of the Skin Microbiome and Association with Microenvironment and Treatment in Canine Atopic Dermatitis*. Journal of Investigative Dermatology, 2016. **136**(6): p. 1182-1190.
30. Favrot, C., et al., *A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis*. Vet Dermatol, 2010. **21**(1): p. 23-31.
31. Hensel, P., et al., *Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification*. BMC Vet Res, 2015. **11**: p. 196.

32. Gonzales, A.J., et al., *Oclacitinib (APOQUEL(R)) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy*. J Vet Pharmacol Ther, 2014. **37**(4): p. 317-24.
33. Gonzales, A.J., et al., *IL-31-induced pruritus in dogs: a novel experimental model to evaluate anti-pruritic effects of canine therapeutics*. Veterinary Dermatology, 2016. **27**(1): p. 34-e10.
34. Olivry, T., et al., *Interventions for atopic dermatitis in dogs: a systematic review of randomized controlled trials*. Vet Dermatol, 2010. **21**(1): p. 4-22.